A CONTRIBUTION TO THE KNOWLEDGE OF ENDOTHELIOMA AND PERITHELIOMA OF BONE.

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INTRODUCTION.—From time to time there have been reported cases of bone tumor showing certain peculiarities of structure which have served to separate them from the ordinary osteo- and periosteal sarcomata on the one hand, and the peculiar tumors or group of tumors classified as myeloma on the other. Such cases were reported in the sixties by Lücke, Kocher, and Billroth; in the seventies by Engelmann, Jaffé, Sudhoff, and others. To Hildebrandt (1891) belongs the credit of collecting these cases from the literature and giving a clear clinical and pathological picture of this affection. His work was based on eight cases, including one of his own. Volkmann (1895), in his exhaustive article on endothelial tumors in general, reported a case of endothelioma of bone, abstracted the previously reported cases, and analyzed the tumors according to their seat and histological structure. Volkmann's conclusions were based upon fourteen cases, one of which (Zahn's second) was evidently a myeloma and should be excluded. Including our own four cases, herewith reported, there are now twenty-three cases available for analysis and generalization. The present work consists in (1) An abstract of the previously

reported cases. (2) Report of four new cases. (3) Pathology of endothelioma and perithelioma of bone; (*a*) general pathology; (*b*) histology; (*c*) histogenesis. (4) Etiology. (5) Clinical history, diagnosis, and treatment.

The following cases classed as endothelioma or perithelioma primary in bone are to be found in the literature. The earlier ones have been already collected in the articles of Hildebrandt, L. Volkmann, and Gaymard, but they have not appeared in English:

CASE 1.—LÜCKE, 1866, reported the case of a woman forty years of age, who complained of lancinating pains and a swelling in the right arm, and on reaching to a high place developed a spontaneous fracture. An elastic tumor rapidly developed. The axillary glands were not invaded. Disarticulation at the shoulder; no recurrence after three and one-half years.

Tumor.—The tumor was covered with healthy skin and atrophied muscle. On section it was soft, of a red color, and contained a large cavity filled with bloody fluid. Microscopically there was a fine reticulum with blood-vessels, supporting bands, and gland-like columns of epithelial-like cells, many of which contained colloid material.

Origin in the marrow cavity.

CASE 2.—KOCHER, 1868, a male, aged sixty-six years, eight months after an injury developed a pulsating tumor, with a systolic bruit, of the frontal and temporal bones.

Under the impression that it was an aneurism the carotid was ligated. Pulsation disappeared but returned, when the growth was extirpated.

The tumor developed between the pericranium and the dura. Microscopically the tumor was very vascular and contained spaces lined with rows of cells and containing blood in their lumina. Marked hyaline degeneration. No metastases.

CASE 3.—BILLROTH, 1869. A male of middle age, with a pulsating tumor of the lower half of one tibia. Amputation. On section, the canal of the lower part of the tibia was filled by the tumor. Microscopically, the growth was very rich in thin-walled blood-vessels, and was composed of epithelial cells. Origin: The blood-vessels of the bone marrow; probably perithelioma.

CASE 4.—ENGELMANN, 1871. A male, forty-eight years old, developed a tumor of the sternum and ribs the size of a man's head. Multiple metastases of lungs and lymph-glands. The tumor was firm, encapsulated, and had cysts containing colloid material.

Microscopically, the tumor was composed of round and elongated alveoli and gland-like columns of cells, with colloid degeneration. En-

gelmann regarded the marrow cells as the origin of the tumors; probably endothelium of lymphatics.

CASE 5.—JAFFÉ, 1874. Male, aged twenty-four years. A pulsating tumor of the left iliac bone developed to the size of a pear in six months.

Partial extirpation; death.

The left iliac bone was extensively invaded by a tumor mass with an alveolar structure and many small cavities. Near the centre these were the size of a pea and red in color.

At autopsy, numerous metastases were found in the lungs and pleuræ. On microscopical examination, the tumor was very vascular and showed an alveolar structure, some of the spaces resembling acini. There were spaces lined with several rows of cylindrical cells and containing no blood-corpuscles.

Origin.—Jaffé thought the inner layer of the periosteum.

CASE 6.—SUDHOFF, 1875. Female, aged thirty-two years, complained of pain in the joints for three years. There was a tumor of certain of the spinal vertebræ and of the sacrum. Death from pressure-myelitis. At autopsy the seventh dorsal vertebra was swollen, the bodies of the twelfth dorsal and first lumbar vertebræ were softened and invaded with a grayish white marrow-like substance. From the tenth to the twelfth dorsal vertebræ a tumor mass compressed the spinal cord. The second, third, fourth sacral vertebræ, the sternum and left femur were also involved. The femur was the seat of a spontaneous fracture.

In structure the tumors were in some places composed of large cells, round or polygonal in shape, with single nuclei and arranged in large alveoli supported by a stroma of fibrous and elastic tissue. In other places the arrangement was tubular, with cylindrical or flat cells and containing a fine lumen.

The origin of the growth was thought to be from the vascular endothelium.

CASE 7.—SCHWEININGER, 1876. A large centrally situated "adenoid" sarcoma of the humerus (sex and age not given). Microscopically the growth showed a plexiform arrangement and gland-like tubules. The origin was thought to be from the endothelial cells of the blood and lymph vessels and lymph spaces.

CASE 8.—V. LUKOVICZ. Male, aged sixty years. For twenty-one months before coming under observation sciatic pain on the right side. When first seen he had a diffuse thickening of the upper part of the right femur. In a short time there developed a rapidly growing tumor of the upper third of the femur, with spontaneous fracture of the latter. Death occurred eight months after the first occurrence of the sciatic pain.

At autopsy there was found a large mucoid tumor which involved two-thirds of the shaft of the right femur. On section the growth had a spongy appearance and contained a number of cysts containing mucoid material. There was extension to the pelvis and metastases in the pleuræ.

Microscopically the tumor consisted of large and small cyst cavities lined with low cubical or cylindrical cells of the epithelial type. The

cavities contained mucus, as did some of the cells. The tumor apparently took its origin from the endothelial cells of the connective-tissue lymph spaces.

CASE 9.—KOLACZEK, 1880. Male, aged eighteen years. A large tumor of the upper part of the left tibia which had developed in five and a half months. The leg was very much enlarged; slight enlargement of the inguinal glands.

Amputation.—The greatest length of the tumor was 22 centimetres and the greatest width 30 centimetres. It consisted of a hard and soft part, the latter containing cysts. The firm portion showed the histological structure of a spindle-cell sarcoma, while the soft portion showed endothelial lined spaces containing no blood-corpuscles.

Origin.—Probably from lymph spaces and vessels.

CASE 10.—ZAHN, 1889. Female, fifty-three years old, had a tumor of the base of the skull with numerous metastases (vertebræ, ribs, and liver). Microscopically the tumor showed an alveolar structure with bands and tubules of epithelial-like cells, some of which showed colloid degeneration.

The tumor was thought to have its origin in the endothelium of the blood capillaries. A second case reported by Zahn (*Beitrage zur Geschwulstelehre, Deutsche Zeitschrift für Chirurgie*, 1885, No. 22), reported as a multiple myeloma, is included in Volkmann's list, but I think that, with the similar tumor of Rustitzky, it should be excluded.

CASE 11.—HILDEBRANDT, 1891. Male, forty-five years of age. In childhood he sustained a fracture involving the right elbow. Nine months before coming under observation he had pain in the right arm; six months before being seen there was swelling of the right arm, and fourteen days before there was a spontaneous fracture. Amputation at the elbow; no recurrence on discharge one month later.

The tumor, which involved the lower end of the arm, was nodular in places, but the joint was intact. There was a fracture of the bone at the seat of the tumor. The latter was the size of a child's head, soft, and on section was red in color, and contained a central cavity, the size of an apple, filled with reddish gray material. The tumor was very vascular. It extended to the periosteum.

Histologically the growth consisted of blood-vessels, usually capillaries, from the sides of which there were cylindrical cells arranged in regular rows, forming tubules. The vessels contained red blood-cells.

Origin.—Stated as the perithelial cells of blood-vessels.

CASE 12.—DRIESSEN, 1893. A male, aged seventy-four years, had pain in the left elbow for two or three years. On admission there was a small tumor of the upper end of the left ulna. The tumor was removed, and there was no recurrence fourteen months later. The tumor was egg-shaped and measured 6 by 4 centimetres, and was firm in consistency. In places it was white, and in others of a dark-brown color.

Histologically the tumor showed both alveolar and tubular arrangements. The cells lining the spaces were epithelial-like, cylindrical, oval, and polygonal in shape. The growth was well supplied with blood-

vessels and fibrous tissue. The tumor cells contained fat and glycogen. Driessen thought the tumor had its origin in the endothelium of the lymph spaces of the bone marrow. There was no apparent connection with the blood-vessels.

CASE 13.—SPIEGELBERG, 1894. Female, aged sixty-two years. No history was obtained. At autopsy there was widespread tumor formation in various bones; the tumors varied from a walnut to a fist in size. They evidently had their origin in the bone marrow. Especially large growths sprang from the right os ilii and from the right metatarsal bone. The ribs and sternum were extensively involved. A small metastasis was found in the spleen; the other organs were free from tumors.

Histologically the tumors showed a well developed fibrous tissue stroma marked in places by the presence of spindle-shaped cells. In this stroma there were large and small alveoli containing cells of the size of ordinary pavement epithelial cells with round, deeply staining nuclei. The cytoplasm stained well with eosin. The cells varied markedly in shape and size; some were the size of ganglion cells. The cells were arranged in rows and cylinders, and between some rows a definite lumen could be made out. Spiegelberg regarded the growth as an endothelioma developed probably from the lymph spaces. Spiegelberg alludes briefly to a second and apparently similar case, without giving, however, either clinical or anatomical details.

CASE 14.—VOLKMANN, 1895. Female, aged seventy years. Two years before admission she noticed a slow growing tumor the size of a walnut on the back of her head. Eighteen months later it began to grow rapidly and was quite soft. On admission there was a soft, elastic, fluctuating, pendent tumor the size of a child's head growing from the occipital region. At one part there was an area of ulceration. On pressure pulsation was felt. At the base one could feel a circular perforation of the skull.

The tumor was extirpated and found to spring from the bone. The dura was normal. Death ten days after the operation. Autopsy. No metastases. The tumor was soft, pale, and marked here and there by reddish areas.

Histologically the tumor presented a groundwork of a spindle-cell tissue, supporting numerous gland-like tubules lined with a single and in some places multiple rows of cylindrical cells which could not be distinguished from cylindrical epithelial cells. These cells had large oval nuclei situated at the base of the cells. Among these high cells there were some cubical and polygonal-shaped cells. The lumina of the tubules were in general round. Some contained colloid or hyaline material. The origin of the tumor was traced to the spindle-shaped cells of the bone marrow, only a portion of which is in relation with the blood capillaries. Volkmann concludes that the cells separated from the vessels to form columns and to develop into gland-like tubules with cylindrical cells.

CASE 15.—MARKWALD, 1895. A male, aged fifty-six years, was taken ill in the spring of 1893 with pains in the back, chest, and joints.

By December, 1893, he was weak, his head rested on his chest, and the abdominal vertebræ were bent backward and to the left side. The deformity increased, and the patient died July 2, 1894. At the autopsy nothing of special interest was found in the internal organs. The head and body were cut in sagittal section in the middle line. The brain and cord were normal. The bones of the skull showed a number of small, reddish-brown, soft, very vascular tumor masses. Similar new growths were present in the bodies of most of the vertebræ, in the ilium, and the long bones of the extremities and the ribs. In the latter the tumors were both periosteal and in the marrow. All the tumors appeared to be of about the same age.

Microscopically, the tumors were composed of a connective-tissue stroma rich in capillaries, with cell masses arranged in rows suggestive of carcinoma. The cells had large, round nuclei surrounded with a considerable amount of protoplasm. The cells often formed long rows. Many of the spaces contained blood. The tumors sprang from the endothelium of the small capillaries and were classed as an intravascular endothelioma. The tumor tissue was not circumscribed, but tended to spread.

Case 16.—Gaymard, 1898. Female, aged nine years. She always had had good health until some months before coming under observation. Five months later she fell from a carriage, striking her head. There was a fracture of the left hip at the trochanter, where a tumor mass was felt. Fifteen days after the fall a small tumor was discovered at the junction of the right frontal and parietal bones. This tumor was soft, and on excision had the appearance of human muscle. Diagnosis. Angiosarcoma of the upper end of the left femur with metastases in the skull. Operation. Excision of the tumor of the skull.

Histologically the tumor was composed of a net-work of vascular tissue, with a delicate connective-tissue framework limiting large alveoli, and between this framework and the vascular spaces containing red blood-corpuscles there were from five to ten rows of round or polygonal cells; thus, a vascular lumen, stratified rows of cells, then supporting connective tissue. Gaymard regarded the cells as endothelial in origin.

Case 17.—Ritter. A female, aged fifty-one years, had pain in the right leg for six months. Three months later there was a swelling of the right leg and foot. Examination showed a fluctuating, pulsating tumor connected with the lower end of the tibia. Operation at the knee-joint. The tumor was spindle in shape; it began 3 centimetres above the ankle-joint, and was 8 centimetres long and 19 centimetres in circumference. Just above the tumor there was an old fracture of the tibia. The periosteum was thickened over the tumor, which in places penetrated the former. On section the tumor was soft and juicy, and of a dark brownish red color. No bone was found in the tumor. No metastases were made out. The tumor was composed of a structure of rather large cells arranged in places in long single rows, in places in solid nests or cords of cells, and in other places, still, in larger and smaller spaces or cavities. In the last case the cells were large, oval,

round, or pointed, and rested against capillary vessels which often contained red blood-cells. There was no membrana propria. The large spaces which contained blood were round, oval, or tubular in shape, and often communicated. Their lining cells rested directly upon capillary walls. The cells contained large fat drops, and some a material staining brown with iodine. The protoplasm of the cells was granular. The nuclei were large and stained deeply.

Origin.—Stated as the perithelial cells.

CASE 18.—BERGER, 1900. Female, fifty-eight years old, was admitted to the hospital in November, 1898, with a pulsating tumor and spontaneous fracture of the upper portion of the left humerus. In the previous June she had transient pains in the lower extremities and pain and loss of use of the left arm. On admission there was a pulsating tumor, the size of a mandarin, in the inferior deltoid region. The neighboring glands were not enlarged, the heart and lungs were negative.

Diagnosis.—Pulsating angiosarcoma of the humerus. Amputation. About two weeks later there appeared a swelling of the left side of the face, which later involved the orbital and frontal regions. At the same time the pains in the lower limbs returned. Some months later a tumor developed in the upper part of the left thigh. In June there was a spontaneous fracture of the superior portion of the left femur. There was pain in the trunk, and on one occasion blood in the urine. The tumors increased in size and the patient was bedridden. The upper part of the humerus, except the head and surgical neck, was destroyed by the growth, which was limited by a capsule which was continuous with the periosteum and separated the tumor from the surrounding soft parts. The tumor was continuous with the medullary tissue of the bone, and was soft, friable, spongy, and of a red-wine color. It contained spaces filled with blood and dark clots.

On histological examination by Dr. Bezançon the tumor was found to be surrounded by a connective-tissue capsule rich in blood capillaries. The tumor proper was composed of alveoli with thin connective-tissue stroma supporting cells of varying size. The thin alveolar walls consisted mainly of blood capillaries from 9 to 10 microns wide, which anastomosed with the vessels of neighoring alveoli, which were sometimes cylindrical, sometimes polygonal, or even round when they were about a lumen. The cells were in the main rather large,—15 to 20 microns in diameter. The cells had clear cytoplasm which stained with neither acid nor basic stains. They contained a single central vesicular nucleus with little chromatin and a large nucleolus. No karyokenesis was observed.

Origin.—Endothelium or perithelium.

There was a marked likeness to the tumor reported by Gaymard.

CASE 19.—STERNBERG, 1901. Female, aged sixty-six years, had pain in the back and knees for fourteen days. She was anæmic and presented the clinical picture of pernicious anæmia, but no blood examination was made. She died two days after admission.

Autopsy.—The body was poorly nourished; no deformities of the

skeleton. The lungs, pleuræ, and heart were negative. The liver showed a number of small nodules. The gall-bladder and bile ducts were negative, as were all the other organs except certain bones. The right femur and humerus, on section, showed scattered, soft, grayish white nodules. The sternum, ribs, vertebræ, sacrum, and cranial bones showed similar nodules.

Sections of the tumors of the marrow of the various bones showed large round, clear, swollen cells with peripherally placed, half-moon or sickle-shaped well staining nuclei. The cell body had a finely granular border, while the inner part of the cell contained one or more vesicles or spaces (fat spaces). In some cells the cytoplasm was transformed into a large vesicle containing finely granular material. The cells were supported by a net-work of fine capillaries forming an alveolar arrangement. Giant cells were found in some places. The tumor cells contained no glycogen. No micro-organisms were found.

PERSONALLY OBSERVED CASES.

CASE 20. (Case I, HOWARD and CRILE.)—*Primary Perithelioma of the Left Humerus ending in Spontaneous Fracture; Non-union of the Fracture. Metastasis on the Tip of the Nose. Amputation of the Humerus and Tip of the Nose; Death on the third day.*

Clinical History (Dr. Crile). *Personal History.*—The patient was a well-built man, sixty-five years of age, and of a sturdy family without any history of malignant disease. He had always been active in business, and in his later years carried heavy responsibilities. There was no history of serious illness except several attacks of appendicitis.

Two years before the fracture of his humerus he fell down an elevator shaft for two stories without serious injury. He had been accustomed to drive a spirited trotting horse, even up to the time of the spontaneous fracture.

Present Illness.—For about two years prior to the fracture he suffered considerable pain in the humerus near the point of the fracture. The pain was not influenced by the weather, exercise, or by pressure, neither by treatment. While tossing a tennis ball preparatory to serving, his arm suddenly snapped and fell helplessly by his side. A temporary dressing was applied by Dr. N. C. Varian, after which he was under the care of his physician, Dr. C. B. Humiston. The fracture was transverse and was easily kept in place. There was nothing unusual in its clinical course excepting the tardy repair On the second and third weeks there

was a fairly good callus, but later this diminished and almost disappeared. At this time I became associated with Dr. Humiston. The tumor of the nose was such as to give the end of that organ the appearance of a greatly exaggerated tippler's nose,—red, tuberous, elongated, and slightly turned up.

On close inspection the numerous blood-vessels increased in density towards the tip, and faded out upward and laterally. There was neither pain nor tenderness. On palpation a distinct pulsation could be made out.

A diagnosis of angiosarcoma was made; a section, under local anæsthesia, was removed and submitted to Dr. W. T. Howard, Jr., who returned the diagnosis of perithelioma.

The fracture was believed to be due to a similar process in the humerus. At the end of eight weeks the humerus at the point of fracture showed pulsation.

Dr. Humiston, assisted by Dr. Hain, Dr. Fitzgerald, and myself, performed the operations.

The patient bore the operations well, but developed some obscure pulmonary symptoms on the third day and died rather suddenly. No autopsy was made.

The arm and the nose were submitted to Dr. W. T. Howard, Jr., for pathological investigation

Pathological Report (Dr. Howard).

(*a*) Small portion of tissue removed from the tip of the nose by Dr. Crile for microscopical examination. The specimen consisted of a small piece of skin and underlying tissue.

On microscopical examination the epidermis was found unbroken, somewhat thinner than normal, but otherwise unchanged. Beneath the skin and entirely unconnected with the epidermis there were a number of large capillaries and blood sinuses of varying size, surrounded by from one to three or four rows of large oval or polygonal cells with faintly staining vesicular nuclei, which usually contained nucleoli. Many of the nuclei showed mitoses. The outlines of most of the cells were very distinct; the cytoplasm was often vacuolar and sometimes finely granular. In many cells it was very obscure. The new growth was not encapsulated and extensively invaded the surrounding tissue. A diagnosis of endothelial hæmangiosarcoma was made, and immediate operation for the growths of both the nose and the humerus advised.

(*b*) On November 21, the tip of the nose and the left upper extremity of this patient were received at the laboratory.

Nose.—The specimen consisted of the end of the nose, including both alæ nasi, and measured 3 by 3.5 centimetres. At the tip there was an elevated tumor nearly round in outline and projecting from 8 to 12 millimetres above the surrounding skin. At one portion there was a small area of ulceration, and at another a globular protuberance .5 centimetre in diameter.

On section the tumor was 1.5 centimetres wide and 8 to 10 millimetres in depth, and of a grayish pink color. Its margins were irregular. At one point the tumor approached but did not invade the cartilage of the nose. The skin and underlying tissues were otherwise unaffected.

Portions of tissue were hardened in Orth's and Zenker's fluids and in alcohol, and stained with hæmatoxylon and eosin, eosin and methylene blue, and Weigert's elastic tissue stain. Sections through the whole growth showed that it was covered with unbroken skin, except at one point where the epidermis was entirely lost; the underlying tissue was infiltrated with red blood-cells, leucocytes, and plasma cells. At this point the tumor was from 1 to 2 millimetres beneath the surface, from which it was separated from the necrotic and infiltrated dermis by a thick layer of fibrous tissue. The new growth was in no way connected with the epidermis or the glands of the skin. It was surrounded by a rather dense fibrous tissue which it infiltrated on all sides. The tumor was separated into a number of well defined but irregularly oval areas by dense, white fibrous tissue bands, which were poor in nuclei and blood-vessels. The new growth was composed of a large number of capillary and venous spaces containing red corpuscles and lined by from one to four or five or more layers of large, round, oval, or polygonal cells with faintly staining nuclei. Here and there were larger and smaller spaces without visible lumina filled with large, flat cells like endothelial plates. Large blood sinuses lined with a single or double row of cells were numerous. No elastic tissue was found in the tumor.

Arm.—The specimen consisted of the left upper extremity. The forearm, hand, and fingers were normal. The arm measured 54 centimetres in length. In its middle third there was a tumor involving the whole thickness of the humerus, the periosteum and a portion of the muscles for a distance of 10 centimetres.

The skin was normal. The tumor was 15 centimetres in its greatest diameter. The muscles were irregularly invaded, the periosteum could not be made out, and a few spicules of bone represented the remains of the shaft of the humerus throughout the extent of the tumor. The marrow cavity, as well as the bone, periosteum, and muscles, was transformed into a homogeneous, pale, grayish-red tissue of a soft spongy consistency. A small amount of blood escaped on section. There were no cysts. The edges of the bone at the upper and lower borders of the growth were rough and irregular, but firm. The new growth invaded the marrow cavity for some distance above and below the main portion of the tumor. The head of the humerus was normal. The elbow-joint contained a small amount of clear fluid. Cultures from the tumor remained sterile.

Small pieces were cut from the various portions of the new growth, and from the humerus and its bone marrow and hardened in Zenker's and in Orth's fluids. Sections were stained with hæmatoxylon and eosin, methylene blue and eosin, with and without Weigert's elastic tissue stain, and with Mallory's connective-tissue stain.

The new growth was composed of a groundwork or supporting tissue, of sometimes thin and sometimes thick branching bands of rather dense, white fibrous tissue. In some places, especially where the growth was invading neighboring tissue, the supporting tissue had a hyaline, homogeneous appearance and contained relatively few elongated nuclei. No elastic fibres were found in this tissue.

The essential structures in the new growth were, however, numerous capillaries and sinuses of varying size containing a varying number of red blood-cells. These spaces were lined with from one to five rows of round, oval, or polygonal cells, with faintly staining and often vesicular nuclei, which often contained nucleoli. Nuclear figures were plentiful.

The cell walls were very prominent, while the cytoplasm was often indistinct and did not take the eosin stain. It was commonly finely granular and often vacuolar. The cells were often arranged in regular rows like glandular epithelium, and in this case were commonly columnar in shape, with their nuclei situated at the end of the cell furthest from the lumen. The tumor cells varied from 8 to 15 microns in diameter.

The blood spaces varied greatly in width, some being filled by a single red blood-cell on edge, while others were from 20 to 30 or even 200 microns in diameter. In some places the growth was alveolar in structure, there being no lumina, but the spaces completely filled with cells of the endothelial type. There was rather free communication between the blood spaces, which varied from long tubules to round spaces. The tubular structures ran in various directions. On cross-section they closely resembled gland ducts lined with cubical or columnar epithelium. In many places, especially where several spaces opened into each other, typical papillary processes were seen. They were composed of a thin layer of supporting fibrous tissue, covered with a single layer of cells.

The absence of a membrana propria was striking, the cells being in direct relation with capillary walls or with the supporting connective-tissue bands. A capillary could usually be traced between the neighboring or adjacent tubules or alveoli, the cells of which abutted the vessel. The spread of the new growth could be readily traced from the cells lining the blood spaces. In many places at the margins of the growth single and double rows of these cells could be traced making their way far out into the neighboring tissue. All gradations could be made out between these cells and the tumor cells. While the relations of the new growth to the capillaries were intimate, positive proof of the origin of the tumor cells from the vascular endothelium was not obtained. The new growth could not be traced to the lymphatic structures, either. The tumor is therefore in all probability to be classed among the so-called peritheliomata whose histogenesis will be discussed later. As the growth advanced, the surrounding tissue, whether bone marrow, bone, periosteum, muscle, or connective tissue atrophied and was infiltrated. The head of the humerus was not invaded. No newly formed elastic tissue was found in the tumor.

A small amount of blood pigment was present in the tumors of both nose and bone. Tests for glycogen were negative.

These growths were identical in structure. From the clinical history and the study of the tumors there is little doubt but that the nasal tumor was a metastasis for that of the humerus. It is much to be regretted that an autopsy was not granted.

Case 21. (Case II, Howard and Crile.)—*Primary Peri-*

thelioma of the Left Humerus with Metastases of the Left Temporal Bone, the Pleuræ, Lungs, and Liver. E. S.; male, aged thirty-one years; white; single; a patient at the Cleveland City Hospital, service of Dr. C. F. Hoover.

In January, 1899, he had a spontaneous fracture of the middle third of the left humerus. The bone apparently knit, but nine weeks later a second fracture occurred at the same place. Shortly after the first fracture the patient noticed a small nodule over the right temporal bone. He died of exhaustion, August 2, 1899, about seven months after the first fracture of the humerus.

Autopsy.—The body was markedly emaciated. The middle third of the left humerus was the seat of a large, soft, grayish red tumor. Occupying the space between the left orbit and the left ear there was a large tumor the size of an orange. The latter growth was continuous with the temporal bone, which was soft and friable. This tumor was soft, grayish-red in color, and quite vascular. The surface of the body and the other bones as far as could be determined were free from metastases. Metastatic nodules from 2 to 10 millimetres in diameter occurred in both pleuræ, both surfaces of the diaphragm and in both lungs, and on the superior surface of the liver. The bronchial glands and mediastinal tissue were extensively invaded. The other organs were without present interest.

Histological examination of bone tumor. Sections made from various parts showed very much the same appearances. The bone tissue was largely replaced by a new growth composed of a fibrous tissue stroma which, in general, was quite thin, often consisting mainly, and sometimes entirely, of single narrow blood capillaries, forming alveolar spaces, which were filled with cells of varying shape and size. In most places the cells lay in direct relation with the capillary walls, which to a great degree formed the boundaries of the alveolar spaces. The latter were round or oval in outline and from a few to 200 or 300 microns in diameter. The cells were from 8 to 16 microns in diameter, and were round, oval, or polygonal in shape. Often they formed large flat plates like endothelial cells. They were often placed in long rows, but only occasionally could a lumin be made out. No columnar cells were found. Many giant cells were present in some places. The cells had large, oval, vesicular nuclei, each with a nucleolus. The

cytoplasm was finely granular and stained well with eosin. The cells were intimately connected with the capillaries. The bone disappeared before the advancing growth. This tumor in structure is a typical example of the so-called perithelioma of Hildebrandt.

The metastases of the pleuræ, lungs, and liver showed a structure identical with that of the original tumor.

Diagnosis.—Primary so-called perithelioma of the left humerus with metastases of the left temporal bone, the pleuræ, lungs, and liver.

CASE 22. (Case III, HOWARD and CRILE.)—*Primary Endothelioma springing from the Lymph Spaces and Channels of the Lumbar Vertebræ, Clavicle, and Ribs, with extensive Metastases. Chronic Cholecystitis with Gall-stones and thickening of the Gall-bladder.* I. M.; male; white; aged forty-five years, entered the Lakeside Hospital, service of Dr. Edward F. Cushing, June 16, 1901, complaining of pain in the left side and back. His family history was negative. He denied syphilis and gonorrhœa. He had always been well until seven weeks before admission, when he was taken ill with pain in the abdomen, left side, and back. His bowels were constipated. The pain was worse at night and ran up and down the back. He was treated by his physician for lumbago. He said he passed less urine than formerly. The patient recalled having had a fall on January 1, 1901, but says he felt perfectly well afterwards until the present illness.

On admission, examination of the heart, lungs, liver, and abdomen were negative. There was no disturbance of the sense of temperature. The spinous processes of the third and fourth lumbar vertebræ were more prominent than normal, and pressure on the lumbar muscles caused great pain. Turning in bed and walking were accomplished with difficulty. In walking, the legs were dragged along with a shuffling gait. In stooping, the back was held rigid. When the head was tapped, sharp pain was felt in the lumbar region.

The urine was clear, of an amber color, sp. gr. 1030, acid, free from sugar. No albumen (albumose not recorded). No casts, a few leucocytes. The patient ate little and steadily declined. On July 5 a small subcutaneous nodule was noticed on

the right side just below the ribs in the posterior axillary line. Later, a similar nodule appeared on the opposite side.

On July 20, a painful swelling of the sternal end of the left clavicle was noticed. Blood examination, July 17, showed leucocytes 10,000 per cubic millimetre; hæmoglobin, 89 per cent. July 21, the leucocytes were 22,000 per cubic millimetre. The patient died July 29, 1901, after having been comatose for three days.

Autopsy two hours after death.

Abstract of the autopsy protocol. The body was 165 centimetres long and very much emaciated. On the left sternoclavicular articulation there was a well-marked tumor mass. The joint was movable and crepitant. Small subcutaneous nodules were present on the chest, abdomen, back, and left buttock. On section they were firm, translucent, and glistening. The sternum, costal cartilages, and mediastinum were negative. The tumor of the left clavicle was firm and translucent and grayish-white in appearance. Similar masses were present in the third and fourth ribs of the right side.

The bodies of the third and fourth lumbar vertebræ were softened and cut with comparative ease; the bone tissue was almost entirely replaced by a grayish-white translucent tissue. The body of the second lumbar vertebra contained an oval nodule 2 by 12 centimetres in diameter, and of a similar appearance. The bodies of the third and fourth lumbar vertebræ were flattened, the periosteum thickened, and in places extensively involved in the tumor tissue. This was especially well marked on the posterior surface of the bones where the tissue was soft and readily compressed. The spinous and transverse processes of the third and fourth lumbar vertebræ were thickened and extensively invaded with tumor tissue. A mass of tumor tissue, 2 by 1 by 1.5 centimetres projected from the spinous process of the third lumbar vertebra into the spinal canal and compressed the cauda equina. The dura was not affected, but the canal contained a large amount of clear fluid. A similar but smaller mass was found opposite the fourth dorsal vertebra; the cord was not compressed at this point. The left psoas muscle, near the bodies of the second and third lumbar vertebræ, was the seat of an irregular tumor mass 3 by 2.5 centimetres in diameter. On section this mass was found to be directly continuous and identical

in structure with the new growth of the vertebræ. As far as could be determined, no other bones were affected. Examination of the brain was not allowed.

The vascular system showed nothing abnormal. A few small nodular masses were found in both lungs. The peritoneal cavity contained 2500 cubic centimetres of greenish yellow fluid. The peritoneum over the intestines was studded with numerous small pale elevated nodules. The liver weighed 1650 grammes. The surface was covered with numerous pale elevated areas from 0.25 to 0.5 centimetre in diameter. The ligaments were thickened and contained similar nodules. On the extreme right border of the liver there was a firm nodule 5 x 3 centimetres. On section the organ was bile stained, and was studded with numerous brown or yellowish, firm, small areas which were sharply defined from the liver tissue. The lobules were visible. The bile ducts were dilated.

The gall-bladder was quite small and its walls very much thickened. On section the walls were dense and firm, the cavity much reduced in size, and contained fifty-five yellowish-brown stones. The mucosa was red, but showed no special thickening and no evidence of tumor formation. The hepatic duct was dilated, the cystic and common ducts normal.

The lumbar, mesenteric, gastrohepatic, peripancreatic, and bronchial lymph-glands were large, firm, and translucent on section. They were extensively invaded by metastatic growths.

The other organs are without present interest.

The tumor was evidently primary in the lumbar vertebræ (possibly the ribs and clavicle), whence metastases occurred by extension into the surrounding tissue (psoas muscle), thence to the lumbar and mesenteric and other lymph-glands, the peritoneum, liver, and lungs.

The macroscopical resemblance of the tumors to carcinoma was striking.

Histological Examination.—Sections of the bones. Bodies of lumbar vertebræ. Sections from the centre of the growth show dense, fibrous tissue stroma rather scantily supplied with blood capillaries containing a variable number of spaces filled with large cells. The cells in places formed long rows, sometimes single, but usually double or even treble. In other places there were round or oval alveolar spaces filled with cells. No lumina

were to be seen. Between the cells, both in rows and in alveoli and the stroma in most places, a definite row of thin flat cells in all respects like the endothelial plates of lymph spaces and vessels could be seen. In a number of instances the development of these lining cells into the tumor could be traced; this occurred by the swelling of both nuclei and cytoplasm, with the transformation of the thin plates into large cells, with swollen vesicular nuclei. The tumor cells varied very much in size, from that of a polymorphonuclear leucocyte to huge multinuclear giant cells. They were usually polygonal, but sometimes round, often oval, and in many cases, especially when lying in single rows in narrow lymph spaces, very much elongated. In general they were large cells. The cytoplasm was smooth or finely granular, and stained faintly with eosin. The nuclei were large and vesicular, with well-marked rims, and contained one or more nucleoli. In many of the large cells from three to six nuclei could be made out. Nuclear figures were numerous. Nuclear and cell inclusions were not uncommon. In sections at the advancing border of the growth in bone the origin of the tumor from the endothelium of the lymph spaces and vessels, especially the perivascular lymph spaces, was evident. Here in the soft bone marrow large alveoli of tumor cells were numerous. Following the proliferation of the endothelial cells of the lymph spaces and lymph vessels there was a growth of dense fibrous tissue. The advancing border of the growth was much more cellular and softer than the older portions. With the growth of the fibrous tissue, stroma resorption of bone occurred.

In sections made through the fourth lumbar vertebra and its periosteum and the surrounding tissue, the spreading of the tumor tissue to the latter could be clearly seen. Sections made from the new growths of the clavicle and ribs showed the same structure described in the vertebræ, except that a better opportunity was given for the study of the origin and spread of the tumor tissue, which could be readily traced from the endothelium of the lymph spaces and lymph vessels, especially from the perivascular lymph spaces.

Lymph-glands, mesenteric and bronchial. In the sections studied, the lymphoid tissue was almost entirely replaced by a new growth made up of large and small alveoli filled with large

cells with large vesicular nuclei. Nuclear figures were numerous. No tubular formations were found.

Liver.—Scattered throughout the liver there were a large number of small metastases situated near the portal systems. They showed the same structure as elsewhere, but the tumor cells were crowded together more closely than in other organs. The liver-cells in many places were shrunken, compressed, and contained a large amount of pigment. In the portal systems which were not involved in the tumor metastases, the bile ducts and the portal connective tissue contained a considerable amount of bile pigment.

Sections of the gall-bladder showed desquamation of the lining epithelium, with dilatation of many of the glands and desquamation of the glandular epithelium. In many places the glands were absent. The wall of the gall-bladder much thickened by the presence of a dense fibrous tissue with scattered areas of round-cell infiltration. No tumor was to be made out, though numerous sections from various parts were examined.

Lungs.—In sections of the lungs the metastases were found mostly above the small bronchi, involving the pulmonary vessels, the peribronchial tissue, and often groups of tumor cells were found in the alveoli. In some places subpleural metastases were found. The pulmonary metastases showed the same structure as the original tumor and the other metastases.

Sections of the omentum showed extensive metastases always along the lymph channels and spaces.

Heart.—Sections of the heart muscle (left ventricle) showed a small metastasis. The spleen and pancreas were negative. The kidneys were the seat of chronic interstitial nephritis.

A study of the gross and microscopical lesions showed clearly (1) That the lumbar vertebræ were the primary seat of the new growth; (2) that the tumor spread first through the vertebræ to the surrounding tissue, thence by the lymphatics to the lumbar and mesenteric lymph-glands, the omentum, the peritoneum, and the hepatic lymph-glands; thence to the liver, lungs, heart, clavicle, and ribs. (3) The new growth was an endothelioma springing from the endothelial cells of the lymph spaces and vessels of the lumbar vertebræ.

Anatomical Diagnosis.—Primary endothelioma of the third and fourth lumbar vertebræ, with metastases in the perivertebral

tissue, the left psoas muscle, the lumbar, mesenteric, and bronchial lymph-glands, the omentum, peritoneum, liver, lungs, heart, clavicle, ribs, and sternum. Slight fibroid tuberculosis of the lungs. Chronic cholecystitis, with gall-stones, and thickening of the gall-bladder. Cultures from the lungs showed Staphylococcus pyogenes aureus and Bacillus mucosus capsularis,—other organs negative.

Case 23. (Case IV, Howard and Crile.)—*Primary Lymph Endothelioma of the Left Femur, with Metastasis in the Inguinal Lymph-Glands. Autopsy not obtained.*—Female, aged eleven years. Consulted Dr. Costello, July 15, 1901, complaining of pain in the left femur just above the knee-joint. There was no history of tumors in her family. The father and mother and several brothers and sisters were well. No history of tuberculosis or syphilis was obtainable. The child had had both measles and scarlatina. The child walked into Dr. Costello's office with a slight limp. There was no increase of pain on walking, bending the knee, or on pressure. On percussion there was deep-seated pain. There was slight symmetrical swelling of the left thigh just above the knee. Pulsation was not noted. On questioning the child, she stated that about June 1 she had a fall while playing in the school-yard. Examination by Dr. Costello showed a small abrasion of the skin below the point of swelling. There was no noticeable enlargement of the inguinal or other lymph-glands. The temperature was 99° F.; the pulse normal. *Diagnosis.*—Osteomyelitis.

Operation, July 17, by Drs. Gallagher and Costello. A longitudinal incision was made through the skin and soft parts, about five inches in length, on the outer surface of the left femur, at the point of swelling, and extending through the periosteum. The subcutaneous tissue was entirely normal in appearance. The periosteum appeared somewhat thickened, but not noticeably congested. The bone was firm but appeared thickened. About a teaspoonful of puriform(?) material was obtained from the marrow cavity. The wound was packed with gauze. There was no discharge of pus. About two or three weeks after the operation there was a slight uniform swelling of the lower end of the thigh. Very exuberant granulations formed in and about the sinus which persisted six weeks after the incision. The thigh became progressively larger, until by November it was the size

of a bucket, the swelling being uniformly round in outline and extending from the knee to near the hip-joint. The inguinal glands became swollen and tender, but no other glands were involved, and no other tumors were apparent. There was no pulsation of the tumor. Springing from the seat of the incision there developed a globular tumor mass the size of a man's head and uncovered by skin over a considerable area. Pain was marked. There was no fracture. She was seen by Dr. Crile in consultation in November.

Sections made from the piece of tissue excised by Dr. Crile showed a dense fibrous tissue stroma supporting occasional strands and alveoli of cells. Many alveoli were large and contained thin elongated cells. Some of the cellular strands were quite long.

The cells were large, of the endothelial type, and had rather large nuclei. Many of the cell collections were evidently in lymph spaces, from the lining cells of which their origin could be readily traced. The alveoli were evidently formed by the multiplication of the endothelial cells of these spaces. The blood-vessels took no part in the new growth.

GENERAL PATHOLOGY.

(*a*) Analysis of the 23 known cases shows as follows:

Seat.—Long bones were involved in 19 cases (humerus 7, tibia 3, femur 8, ulna 1); all the long bones, 1, flat and spongy bones in 15 cases (most of skull bones 1, base of skull 2, temporal and frontal bones 2, iliac bone 2, sternum 4, vertebræ 4).

Size.—The tumors were large in 11 cases, of moderate size in 7, and small in 5 cases.

Thirteen were said to be soft, 5 hard, and 5 elastic.

On section, the prevailing color was red or gray red.

Cysts of varying size, usually containing bloody fluid, were found in 8 cases. Of the 16 cases involving the long bones, spontaneous fracture occurred in 7.

In most cases the growth started in the central portion of the affected bone, spread along the marrow cavity, through the bone, and in several cases into the surrounding tissues.

The tumors were quite vascular, and several of the older cases were mistaken for bone aneurisms; seven were said to pulsate.

Metastases occurred in over one-half the cases (14).

In 8 cases the tumors were single and without apparent metastases.

In the 13 cases in which multiple tumors are known to have been present, in only 4 were the bone tumors single. In these 4 cases (Engelmann, Jaffé, von Lukoviez, our Case I), the lungs and pleuræ showed metastases in 3, the primary growths being in the sternum and ribs, left os ilium, and left femur each in 1 case; in the fourth case a primary tumor of the left humerus gave rise to a secondary growth on the nose.

In the remaining cases there were multiple growths in several bones, with metastases in some of the internal organs in 4.

A synopsis of these 9 cases shows as follows: Sudhoff's case, multiple tumors of the dorsal, lumbar, and sacral vertebræ, sternum, and left femur; Spiegelberg's case, right os ilium, a metatarsal bone, sternum and ribs; Marchwald's case, skull, most of the vertebræ, ossa ilia, ribs, and long bones of the extremities; Gaymard's case, left femur and skull; Berger's case, left humerus and femur and the skull (frontal bone); Sternberg's case, right humerus and femur, the sternum, ribs, and several vertebræ; Zahn's case, skull, vertebræ, and ribs; our second case, left humerus and the skull (left temporal bone); our third case, the lumbar vertebræ, clavicle, and ribs. Certain bones were affected with great frequency, the bones of the skull, the vertebræ, the sternum, the ribs, and the femur being the ones most often involved.

Certain combinations of bones stand out prominently; for instance, the skull, the vertebræ, and the ribs, and sometimes the sternum being affected together. The humerus and the femur were simultaneously affected in two cases. In some of these cases it is pointed out in the clinical histories that the tumors apparently involved certain bones after others, but in some instances the tumors of the various bones appeared about the same time and were of apparently the same age. For some cases, at least, it seems not improbable that the tumors started in several bones at the same time, that is, that a number of independent malignant tumors of the same structure originated simultaneously in different bones. Opposed to this view are the fact that malignant tumors rarely originate in multiple foci and the probability that the bone tissue offered a more suitable soil for the growth

of wandering tumor cells than certain other organs to which the cells were also carried. In two of these cases the visceral metastases were inconspicuous, while in the remaining two cases they were wide-spread.

The other five cases of multiple wide-spread tumors of bones, like the myelomata, failed to show visceral metastases and the presence of tumors except in bone. Eleven cases are known to have died; in all but one of these an autopsy was obtained. The growth was rapid in nine cases. The growth of the tumors, when small and not involving the viscera, was associated in many cases with prostration and the usual symptoms of emaciation and cachexia. No special blood changes have been noted. Albumosuria was not mentioned in the histories of any of the cases, and was probably not looked for.

Histology.—The histological descriptions of the earlier cases are not very full, but a conformity to two general types is clear; (*a*) vascular tumors with alveoli filled with cells of various types, and (*b*) gland-like structures lined with single, double, or multiple rows of round, oval, polygonal, or even columnar cells of the epithelial type. In some tumors there were both alveolar and tubular structures. Giant cells may be present in both varieties. In both types the relation between the tumor cells and the blood capillaries is usually intimate and conspicuous. In many cases the tumor cells lie against the capillaries, which course between rows of the former. The blood capillaries may contain much or little blood; often they are compressed by the tumor cells. The alveolar walls are in many instances composed entirely of capillaries, while in others the tumor cells are supported by an abundant fibrous tissue stroma. The latter was especially well marked in our Case 3. The gland-like structures—tubular endo- and perithelioma—often form long tubules, and may contain blood. In some tumors the fibrous tissue was scanty, while in others it was plentiful and rich in nuclei and spindle-shaped cells. As far as is known, it is composed of white fibrous tissue. The tumor cells are prone to degeneration, and there are instances of fatty, colloid, hyaline, and myxomatous change. Ritter and Driessen demonstrated glycogen in the tumor cells in their cases. The iodine test for glycogen was negative in our Case 1.

Many of the tumors in bone were not sharply marked off from the marrow tissue. The histological structure is entirely

unlike that of myeloma, from which it is readily distinguished. The cells and their arrangement, however, differ rather widely, and this is readily understood when their diverse points of origin are considered.

(*c*) *Histogenesis.*—From analysis of the cases available at the date of his article, Volkmann concluded that these tumors had their origin as follows:

From the endothelium of the lymph sinuses, 4 cases (Lücke, Driessen, Engelmann, and von Lukovicz); from the endothelium of blood capillaries and the perithelial cells, 6 cases (Kocher, Kolaczek, Hildebrandt, Zahn, Jaffé, and Billroth); from the endothelium of lymph channels and blood capillaries, 2 cases (Schweininger and Volkmann); unclassified, 1 case (Sudhoff).

While we do not believe that it is possible to accurately classify these cases according to their histogenesis, a careful study of each leads us to think the following is approximately correct, and as near the truth as it is now possible to arrive. From the perithelial cells of Waldeyer, or the endothelium of perivascular lymphatics, 12 cases (Lücke, Kocher, Billroth, Jaffé, Hildebrandt, Gaymard, Ritter, Berger, Sternberg, and Howard and Crile, Cases I, II, and V); from the endothelium of blood capillaries, 2 cases (Zahn and Markwald); from the endothelium of the ordinary lymph vessels and lymph spaces, 7 cases (Engelmann, Kolaczek, von Lukoviez, Driessen, Spiegelberg, Volkmann, Howard and Crile, Cases III and IV); from the endothelial lining either of the blood capillaries or the lymph vessels, two cases (Sudhoff and Schweininger). If the above is correct, one-half of these tumors are perithelial in origin, while the other half are derived from either the blood or the ordinary lymph-vessel endothelium. The term perithelioma was first applied to certain of these tumors by Hildebrandt. That the tumors in question arise from the perithelial cells of Waldeyer, cells found in relation with the small blood-vessels of certain organs, notably the testis, is by no means proven. As Driessen points out, these cells have not been demonstrated about the blood-vessels of either bone or periosteum. Morphologically, the cells of these tumors are of the endothelial type, and like endothelial cells they lack apparently the property of secreting intercellular substance. Hence it is fair to conclude that they are not of the ordinary connective-tissue type. This being so, it is evident that the tu-

mors classed as peritheliomata must take their origin from either the endothelium of blood capillaries or from the endothelium of the perivascular lymph spaces.

That tumors of the same structure as the so-called bone peritheliomata may arise from the endothelium of blood capillaries, we have had recent evidence in an endothelioma of the breast removed by Dr. Crile, in which there were both closely filled alveoli and tubular structures often containing blood and corresponding exactly with the structure of the tumors of our Cases 1 and 2, which would be classed among the peritheliomata by Hildebrandt and others. In this breast tumor some of the blood capillaries were more or less completely filled with proliferated endothelial cells. In other places the mode of development of the tubular structures could be directly traced from proliferated blood capillary endothelium, the newly formed cells protruding from the capillaries, and forming short or long rows in the surrounding, but otherwise unchanged, connective tissue. The perivascular lymph spaces played no apparent part in the process. The presence of blood in the spaces of the so-called peritheliomata does not prove that these tumors spring from the blood-vessel endothelium, for its presence is readily explained by hæmorrhage, large areas of which are not uncommon; contrariwise, the absence of blood in the spaces cannot be taken as an argument against the blood-vessel endothelium as the origin of certain of these growths.

We are inclined to agree with the opinion of Driessen, Perth, Hildebrandt, and others that the so-called perithelium is in reality the endothelium of the perivascular lymph spaces.

We have not been able to make out in sections of bone marrow any cells which could be classed as the perithelial cells of Waldeyer. In the bone marrow the blood capillaries show no such cells, and are not accompanied by perivascular lymph spaces, which can, however, be made out about the small arteries and veins. Hence we would include among the so-called bone peritheliomata those tumors springing from these cells, as distinguished from the lymph endotheliomata derived from the endothelium of the ordinary lymph spaces and lymph vessels, *i.e.*, those not immediately about the blood-vessels. Judged by the study of our own material, derived from tumors of bone and other organs, it is not possible in most cases to decide whether

a given tumor springs from blood-vessel endothelium or perivascular lymph space endothelium (perithelia).

Apparently, there may develop from the endothelium of either of these two places growths of identical structure; that is, the endothelium of either situation may give rise to endothelial cell growths composed of either completely filled alveoli or of tubular spaces (with or without blood-cells in the latter) in which both alveoli and tubular spaces are separated and supported by blood capillaries in direct relation with the tumor cells. The chief difficulty in diagnosis here is due to the fact that growths developing from blood capillary endothelium may form alveoli by proliferation inside the vascular lumen, the alveolar boundaries being furnished by previously existing or newly formed capillaries, or the proliferating endothelial cells may break through the blood capillaries and form either tubular or alveoli structures. Unfortunately, these tumors are not presented for examination in their earliest stages, and one cannot say whether a growing portion of the tumor is derived from the cells of the vessels or spaces in which proliferation is taking place, or the proliferating cells are transported tumor cells from older portions of the growth.

At the present time we cannot certainly distinguish but two varieties of endothelioma of bone: (1) those derived from the endothelium of blood-vessels and perivascular lymph spaces, and (2) those springing from ordinary lymph vessels and spaces, and not immediately connected with blood-vessels. Of our own four cases, Nos. I and II belong to the first and Nos. III and IV belong to the second variety. These two varieties of tumor are characterized by unmistakable differences. The first, with their multiple rows of cells in alveolar or often in tubular arrangement, sometimes containing blood and always bounded by blood capillaries, stand out in marked contrast to the larger and smaller alveolar collections of cells which more or less completely fill the lymph spaces and lymph vessels from which their origin is so readily traced.

The second variety of bone endothelioma much resemble carcinoma in macroscopical and in microscopical appearances, and no doubt the cases of so-called primary carcinoma of bone belong to this group.

Borrman's division of these tumors into two classes—peri-

theliomata and peri-endotheliomata, the first with a radial perpendicular and the second with a concentric arrangement of many layered superimposed cells about the vessel walls—is of doubtful value. The endotheliomata of bone dealt with in this article are not to be confounded with the so-called tubular perivascular sarcomata, types of which are the cases recently reported by Low and Lund.

Of the single bone tumors forming metastases in the other organs, two, as said before, had their origin from the perithelium, and two from the endothelium of lymph-space vessels. The nine cases of multiple bone tumors had their origin as follows: perithelium or blood-vessel endothelium, 6; endothelium of ordinary lymph spaces and vessels, 2; blood or lymph vessels, 1. Both of the tumors thought to be derived from the capillary endothelium and four of the peritheliomata formed multiple bone tumors, and a majority of the peritheliomata showed multiple growths.

Etiology.—Sex is without much influence; 12 cases were in males, 10 in females, and 1 sex was not recorded. These tumors occurred once each at 9, 11, 18, 25, 31, and 52 years; there were 5 cases between 40 and 50, 5 between 50 and 60, and 7 cases over 60 years. A history of previous injury was obtained in 6 cases. Further than this nothing definite is known of the cause of these growths. Without wishing to lay too much stress upon the observation, we must say that in studying sections of our Case III we were impressed with the readiness with which the proliferation of the endothelium of the lymphatics would be explained by the assumption of the action of micro-organisms or their toxines. As was necessarily the case, pictures were seen which were quite similar to those seen in the lymphatics in typhoid and other processes as pointed out by Mallory. In this connection, it is also of interest to recall the observations of the proliferation of endothelial cells of lymphatics with the formation of tubules by v. Notthaft and considered by him due to an infection in a case of pseudo-leukæmia, and the conclusions drawn by Boivard by which he excludes tumor formation in his case of splenomegaly with proliferation of the endothelium of the lymph sinuses of the spleen, abdominal lymph-glands, and perilobular lymph channels of the liver. In our own case we were struck with the idea that had micro-organisms or their toxines acted on these endothelium of the lymph vessels and sinuses, identical

changes must have been produced. Micro-organisms and bodies which might be taken for them have not, however, been observed in these growths. It is to be hoped that the attention that endothelial cells are now receiving may soon throw some light upon the etiology of these growths.

Relation of endo- and peritheliomata to bone aneurisms. Pulsation of the tumors was noted in seven cases. Hildebrandt, who has carefully reviewed the subject of the relation of bone aneurisms and malignant tumors of bones, concludes that true bone aneurisms are rare, and that a pulsating bone tumor is to be regarded as malignant, probably sarcoma. Roughton, who has recently written on the subject, reaches the same conclusion.

CLINICAL (DR. CRILE).

The clinical history and aspects of endo- and peritheliomata of bone present in general a similarity to the general type of osteosarcoma. Certain differences and a few well defined distinctions are apparent on closer study. The number of cases collected (23), which for the purpose of a more minute analysis might readily be said to be insufficient, reveals in certain directions a persistence of a few distinct characteristics, so that a deduction from this compilation of the symptoms, course, and termination of these neoplasms may be fairly assumed to accord with their general clinical anamnesis.

Sex.—In the foregoing tabulation of endotheliomata of bone, the sex is given in twenty-two cases, of which twelve were males and ten females. This proportion is not in correspondence with that found by Gross in sarcoma of bones. In a collection of 149 cases of osteosarcoma, he found that men were by 17 per cent. more frequently affected.

Age.—In marked variance with sarcoma in general is the age at which endo- and peritheliomata of bone are found to occur. In ordinary sarcoma of bone, although no age is exempt, children and young adults are most frequently affected. Butlin states that young adults of both sexes, from fifteen to twenty-five years of age, are much more liable to the disease than persons at the extremes of age, while, according to Volkmann, osteosarcoma usually develop during the growth of the individual, most commonly about the twentieth year, very rarely after the fortieth. Gross, in a tabulation of 147 cases of osteosarcoma in which the

age is given, found that in 68 per cent. these tumors developed before the thirtieth year, and in 32 per cent. after that period. From his table it can moreover be ascertained that 85.7 per cent. of these growths occurred before the fortieth year and but 14 per cent. after that time. Paget, in a collection of nineteen cases of osteosarcoma of various bones, reports the following:

In five cases	the growths occurred	at the age of	10 to 20 years.
In nine	"	"	"	20 to 30 "
In four	"	"	"	30 to 40 "
In one case	"	"	"	40 to 50 "

To this table may be opposed that of bone endotheliomata, the comparison between the two from the similarity of numbers in both being the more striking. In a tabulation of the cases of bone endotheliomata with respect to age, one finds that:

In one case	the growth	occurred at the age of	9 years.
In one	"	"	"	11 "
In one	"	"	"	18 "
In one	"	"	"	25 "
In one	"	"	"	12 "
In one	"	"	"	31 "
In one	"	"	"	32 "
In four cases		"	"	40 to 50 years.
In three	"	"	"	50 to 60 "
In six	"	"	"	60 to 70 "
In two	"	"	"	70 to 75 "

In this tabular arrangement it is to be noted that but five cases, or 26.13 per cent. of bone endotheliomata, occurred before the age of forty and 14 cases, or 73.87 per cent., after that period, while in the table of osteosarcoma of Paget, 18 cases out of 19, or 95 per cent., are found to have developed before the fortieth year, and but one case, or 5 per cent., between the fortieth and fiftieth year. In Gross's collection of 147 cases, as already mentioned, 85 per cent. occurred before the fortieth year, and 15 per cent. after that period. In summary:

Before the Fortieth Year.	After the Fortieth Year.
Paget's table (osteosarcoma), 95 per cent.	5 per cent.
Gross's table (osteosarcoma), 85 "	15 "
In endotheliomata of bone, 26 per cent.	73 "

As to the age, bone endotheliomata are at variance with osteosarcomata, and in accordance with carcinomata.

Cause.—In the majority of the cases there is no apparent cause. Among the cases in which the occurrence of trauma is mentioned in connection with the appearance of tumor is that of Kocher, in which a pulsating tumor with a systolic bruit developed eight months after an injury from a flail in the right frontotemporal region. In Hildebrandt's case, a male, forty-five years of age, the endothelioma was found in the lower part of the arm above a fracture of the right elbow which had been sustained in childhood. Similarly, in the case of Ritter, a female, fifty-two years old, bore the evidence of an old fracture of the tibia, above which was situated the tumor. In another case presenting primary endothelioma in the clavicle, ribs, lumbar vertebræ, the patient had sustained a fall six months previously. As a whole, injury cannot be stated to be an etiological factor of much importance.

Bones Affected.—The predilection of endotheliomata of bone like that of osteosarcoma is for the long bones of the appendicular skeleton. In the 23 cases collected, the exact position of the primary involvement is given in 20, in the other three cases a number of bones were found to have been involved, and the seat of primary origin is either not mentioned or could not be definitely determined. The various bones were affected as follows:

Humerus, 5 times; ulna, 1 time; iliac bones, 1 time; femur, 4 times; tibia, 3 times; head, 3 times; vertebral column, 2 times; sternum and ribs, 1 time; other bones, 3 times.

The appendicular skeleton was involved in 14 cases, the axial skeleton in 6 cases, a proportion of approximately 2.

1. In the appendicular skeleton the upper extremity was affected six times, the lower extremity eight times. Deducting the one case in which the iliac bones were the seat of the malignant growth, it is seen that the long bones of both the upper and lower extremity were equally affected. The single bone most frequently affected is the humerus, there being five cases out of 20, or in 25 per cent. Femur and tibia are next in the order of frequency, each being involved four times, or in 20 per cent.

In osteosarcoma the favorite seat of these malignant growths is the femur and tibia, with by far the greater preponderance in favor of the former, as can be gathered from the table of Gross. Out of 165 cases analyzed,

The femur was the seat of the disease in 67 instances.
The tibia " " " 46 "
The humerus was the seat of the disease in 25 instances.
The fibula " " " 13 "
The ulna " " " 7 "
The radius " " " 6 "
The radius and ulna were the seat of the disease in one instance.

Volkmann, in writing of osteoid or subperiosteal sarcoma, states that these growths are especially encountered in the knee ends of the femur and tibia, and Butlin says that central sarcomas attack the same bones as the subperiosteal variety, so that they may be considered in the same manner and order. He asserts that "the long bones of the lower extremity are much more liable to malignant disease than the long bones of the upper extremity; the femur and tibia are the most frequently affected of all the long bones, the tibia perhaps rather more often than the femur, while the fibula is very rarely attacked. The humerus comes next to the tibia and femur in liability to the disease; the radius is not often attacked, and the ulna so seldom that it is difficult to collect any number of cases of ulnar sarcoma. Treves gives his opinion to the effect that the bones of the lower extremities are more frequently attacked than those of the upper, probably on account of their greater liability to injury; and the lower end of the femur and upper end of the tibia are more commonly affected than the other extremities of these same bones probably for the same reason, that the knees are more often exposed to trivial injuries than any other parts of the lower limbs. In osteo-sarcoma it has been noteworthy that the part of the bone affected is the epiphyseal end. Senn remarks that "sarcoma is found most frequently in that part of the bone where the circulation is most active,—that is, in the epiphyseal extremities of the long bones, and in the inner layer of the periosteum, the cambium." Gross also states that sarcoma of the long bones evince a great predilection for the articular extremities, and the majority develop in the spongy tissues of the epiphysis. In periosteal round-celled sarcomas, however, the same writer says the shafts of the long bones are much more frequently affected than the epiphyses.

In endotheliomata a similar predisposition is apparent, the site of the neoplasm being for the most part near the articular or epiphyseal extremity of the bone, where the vascular distri-

bution is greatest. The exact position as given by the various authors is as follows:

Lücke	Humerus.	Middle.
Billroth	Tibia.	Lower half.
Schweininger . .	Humerus.	Not given.
V. Lukovicz . . .	Femur.	Upper third.
Kolaczek	Tibia.	Upper part.
Hildebrandt . . .	Humerus.	Lower end (near elbow-joint).
Driessen	Ulna.	Upper end.
Gaymard	Femur.	Upper end.
Ritter	Tibia.	Lower end.
Berger	Humerus.	Upper portion.
Crile	Humerus.	Middle third.
Crile	Femur.	Lower third.

The exact point of origin of the endotheliomatous tumors, not unlike osteosareoma, is either from the medullary eanal of long bones or the spongy tissues of flat bones, *i.e.*, eentral, or on the other hand from the periosteum, *i.e.*, subperiosteal. The great majority of eases are of the central variety. Sueh are the cases of Lücke, Billroth, Engelmann, Sehweininger, Driessen, Volkmann, Berger, ete. Among the subperiosteal endotheliomata is to be noted espeeially the ease of Jaffé. In Markwald's ease, tumors of both the eentral and subperiosteal variety were found.

Symptoms: Pain.—The symptoms of osteo-endotheliomata are identical with those of all osteosarcomata. Pain in these neoplasms is neither eonstant nor present in all eases, its presenee being dependent in most instanees upon pressure on or on the involvement of a nervous trunk. It is for this reason variable in character, its onset, duration, degree, etc. Tanaka, in writing of the clinieal symptoms of endotheliomata in general, states that these tumors usually pursue a painless eourse. In central endotheliomata there is probably more often pain than in the subperiosteal variety, it commonly preeeding the appearanee of the tumor for several weeks or months.

Tumor Formation.—The appearanee of swelling or tumor formation makes itself evident at different stages of the disease. In central endotheliomata no enlargement or growth may be pereeptible to either inspeetion or palpation, a spontaneous fraeture from the erosion of bone giving the first indication of the probability of an existing neoplasm. In other cases, however,

an enlargement of the affected bone becomes apparent, and especially so in the subperiosteal variety, in which the tumor formation forms the first reliable clinical symptoms. When first appearing, the tumor is of small size, and in the great majority of cases is reported on as not having increased rapidly in size, usually only attaining the size of a child's head. Pupovac states that a slow growth is characteristic of endotheliomata. In certain cases, as in those of Lukovicz and Volkmann, the growths, after having been in a state of quiescence for some time, suddenly acquired a tendency to proliferate rapidly. In Liicke's case a rapid increase in the rate of growth occurred after the bone had spontaneously fractured.

Capsule.—The demarcation between the tumor and surrounding tissues is in most instances established by a capsule. In the central growths of osteosarcoma, this capsule is either bony, membranous, or partly bony and partly membranous, while in the subperiosteal tumors it is always membranous when present. In endotheliomata of bone, the capsule, when mentioned, is usually stated to have been of a fibrous nature. Hildebrandt, however, refers to a bony capsule in bone endotheliomata, which he states to be formed from the periosteum. The statement that such a bony capsule is a new formation is somewhat problematical, as in osteosarcoma it is known to be a resulting derivative from the expansion of the cortical portion of the bone. This expansion of bone is caused by the invasion of the malignant growth, the tumor being thereby encased in a bony shell. The membranous capsule is derived from the periosteum, and probably to some extent, also, forms other connective tissues in the near vicinity of the bone and atrophied portions of muscles. Its thickness at times characterizes its most distinct attribute, which tends to hold the growth of the tumor in abeyance. Capsule formation in all endotheliomatous tumors has been frequently observed. Kolaczek, in a collection of 78 cases of endotheliomata affecting all the various tissues, states that in over one-half of these a capsule was present. Nasse, in an enumeration of 31 cases of endotheliomatous tumors of the salivary glands, asserts that in but one case was the capsule absent. Volkmann also gives the capsule a prominent position in the description of these neoplasms. The capsulation of these tumors is clinically of great importance, as it limits the growth of the new formation, and

prevents early metastasis and general dissemination. When this investing membrane ruptures, the tumor may suddenly acquire rapid proliferative properties; the degree of its malignancy is thereby accordingly increased.

In their configuration these tumors correspond closely with the osteosarcomata in general, their contour being in part dependent on their situation and point of origin. In central osteosarcoma, whether situated on the epiphysis or diaphysis, a spherical or globular shape is usually found. In the subperiosteal variety, when situated on the shaft, a spindle-shaped enlargement has been more often noted when at or near the articular extremity, somewhat pyriform swelling. This variety, moreover, never enlarges the bone equally in all directions, but merely produces a swelling on one aspect, and little or none on the opposite side. In central sarcoma, the tumor formation may also affect only one side of the bone; but in other instances, the cortex of the bone becomes expanded from the pressure of the growth of the neoplasm, and it bulges out on all sides. Endotheliomata of bone conform in these characteristics with osteosarcoma. Similarly, also, in the character of their surface, which is usually smooth and even, although in certain instances it has been observed to have been lobed nodular or tuberous, as in the case described by Hildebrandt. At times all configuration is lost, and there results from the extensive infiltration of the contiguous tissue, as in one of our cases, a diffuse growth and somewhat general enlargement of the part.

Pulsation.—The occasional occurrence of pulsation in these tumors has in several instances, as in the case of Kocher, given rise to the erroneous diagnosis of aneurism. In this case not only was pulsation present, but also other symptoms pathognomonic of aneurism, viz., a systolic bruit compressibly of the tumor by both direct pressure, and especially upon compression of the carotid artery of that side. Ligation of the artery, moreover, caused a total disappearance of both the pulsation and systolic bruit, which persisted for twelve days, when a faint pulsation but no murmur again reappeared. In one of our own, and in other cases reported by Lücke, Jaffé, and Billroth, both a pulsation and systolic bruit were present. In other instances, however, while a pulsation is described, no mention is made of the systolic bruit or other murmurs. The great vascularity of these tumors in

which pulsation was noted probably explains this occurrence. (Cases of Kocher, Jaffé, Berger, etc.) In others, as in the case of Ritter, blood spaces which communicated with each other are especially remarked upon.

Spontaneous Fracture.—Spontaneous fracture was noted in seven cases out of thirteen, in which the long bones of the appendicular skeleton were affected. Three times it occurred in the humerus and three times in the femur, and in one case, that of Berger, both the humerus and femur spontaneously fractured, the latter being the seat of metastasis. As already stated, spontaneous fracture at times gives the first indication of the existing neoplasm. It may occur without any premonitory symptoms, being the result of an erosion or pressure atrophy of the bone caused by the growth of the tumor. Theoretically, spontaneous fracture should occur only in central endotheliomata, the subperiosteal variety of these tumors, for the reason that they extend in an outward direction, and do not tend to invade the bone, and seldom, if ever, give rise to its occurrence.

Metastasis.—While Gross found that in osteosarcoma, metastasis occurred in 40.06 per cent., we note that in bone endotheliomata it is reported on in 63.64 per cent. of the cases. The organs which are most liable to metastasis are alike in all sarcomata, the lungs and the various bones of the skeleton. The spleen, liver, and lymphatic glands are more rarely affected. The greatest predilection for metastasis from endotheliomata of bone seems to be the bony skeleton; thus, in fourteen cases in which metastasis occurred, the bones were affected nine times, the lungs four times, the liver three times, and the lymphatic glands twice, and the spleen but once.

Diagnosis.—The diagnosis of osteo-endotheliomata cannot during life, from a clinical stand-point, be definitely established, as these neoplasms, as has already been repeatedly mentioned, conform in their essential characteristics with the osteosarcomata. Hildebrandt says that these tumors show no clinical differences. Symptoms entirely pathognomonic of bone endotheliomata which would serve for a differential diagnosis between the two do not exist. Among the differential characteristics may be mentioned the age at which these respective tumors are liable to appear. In patients of over forty years, it is recalled, endotheliomatous bone formations are more common in those whose age is below this

period, while the reverse is the more common occurrence of endotheliomata; and the fact that numerically cases of osteosarcoma are more often found, however, counterbalances any value which may be attached to this distinction. The other symptoms, such as pain, their situation, rate of growth, nature, and configuration of the tumor, metastasis and cachexia either singly or collectively, do not clinically serve to more clearly elucidate the nature of the given growth, whether it be a sarcoma or endothelioma. From other affections with which they may be confounded, the differential diagnosis is the same as for osteosareoma. These are carcinoma, aneurism, if pulsation and its other pathognomonic symptoms be present, other bony tumors and the various inflammatory diseases of bone, periostitis, osteomyclitis, tuberculosis, and syphilis. The diagnosis from carcinoma, even with a microscopical examination, is at times difficult, much the more so from the clinical stand-point. Aneurism, also, may in rare instances so resemble these malignant tumors that it is impossible to differentiate them. Hildebrandt and Klebs each mention a case which, from its gross appearance, was stated to be an osteo-ancurism, and microscopically shown to be an osteosareoma.

Concerning the prognosis of bone endotheliomata, but little can be said, as the experience with the same has as yet been too scant. The prognosis may be stated as favorable in all cases in which an operative treatment can be safely instituted. In tumors of the vertebral column and in those of the base of the cranium, where incision cannot be made, the fatal course of the disease can avowedly not be arrested. Metastasis also renders the prognosis unfavorable. Tanaka says, regarding the prognosis, that it is only favorable in those cases in which it is possible to eradicate all of the diseased tissues. When a diffuse infiltration is present, the chanees for a complete extirpation of the disease and an ultimate recovery are markedly increased. In such cases not only the parent growth has to be removed, but also all the metastatic processes which radiate from it and are found in the surrounding tissues.

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